

REMARKSRejection of the claims under 35 USC §112:

Claims 14-26 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The action states that the claims encompass a genus of unspecified chelators and polymers capable of associating with a polynucleotide. The Action suggests, on pages 4 and 8, that the specification only provides sufficient description of a chelator-polycationic polymer. Accordingly, Applicants have amended claim 14 to cite that primary amine-containing molecule is polycationic and that the chelator is capable of forming a non-covalent coordinate bond with a primary amine. Support for the amendment can be found in the specification on page 17 line 25 to page 18 line 18, and in example 15. Chelators, including crown ethers, known to form non-covalent coordinate bonds with primary amines are readily available in the art as evidenced by March "Advanced Organic Chemistry" Wiley and Sons (attached).

Claims 14-26 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. Applicants believe the amendments to claim 14, described above in response to the written description requirement, are sufficient to overcome the rejection based on the enablement requirement.

Rejection of the claims under 35 USC §102:

Claims 14-26 have been rejected under 35 U.S.C. 102(b) as being anticipated by Kayyem et al. WO 96/11712. Applicants respectfully disagree. Kayyem teaches that a polychelator-polycation can be used to condense DNA. Metal ions, which are able to be coordinately bound by the chelators, can then be added to the DNA/polycation complex in order to co-deliver the DNA and the metal ions. In contrast, Applicants claim forming a complex of DNA and amine-containing polycation and then associating a chelator with amines on the polycation. The attached drawings illustrate the difference between the teaching of Kayyem and the invention claimed by the Applicants. Applicants respectfully request reconsideration of the 102 rejection.

Rejection of the claims under 35 USC §103:

Claims 14-26 have been rejected under 35 U.S.C. 103 as being unpatentable over Kayyem et al. in view of Hnatowich et al. U.S. Patent No. 5,980,861. Applicants respectfully disagree for the reasons stated above in response to the 102 rejection. Applicants respectfully request reconsideration of the 103 rejection.

Double Patenting:

Claims 14-26 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 6,818,626. Applicants respectfully disagree. Claims 1-11 of '626 encompass a polymer in which association of the polymer with a nucleic acid is dependent on the presence of metal cations (see attached illustration). In the instant application, association of the chelator with the nucleic acid is not dependent on the presence of metal cations. Claims 12-17 of '626 encompass metal cation dependent association of a second polymer with a first polymer (see attached illustration). The instant invention claims association of a chelator with a polycation through coordinate bonding of an amine on the polycation. Applicants request reconsideration of the double patenting rejection.

The Examiner's objections and rejections are now believed to be overcome by this response to the Office Action. In view of Applicants' amendment and arguments, it is submitted that claims 14-16 and 18-26 should be allowable.

Respectfully submitted,



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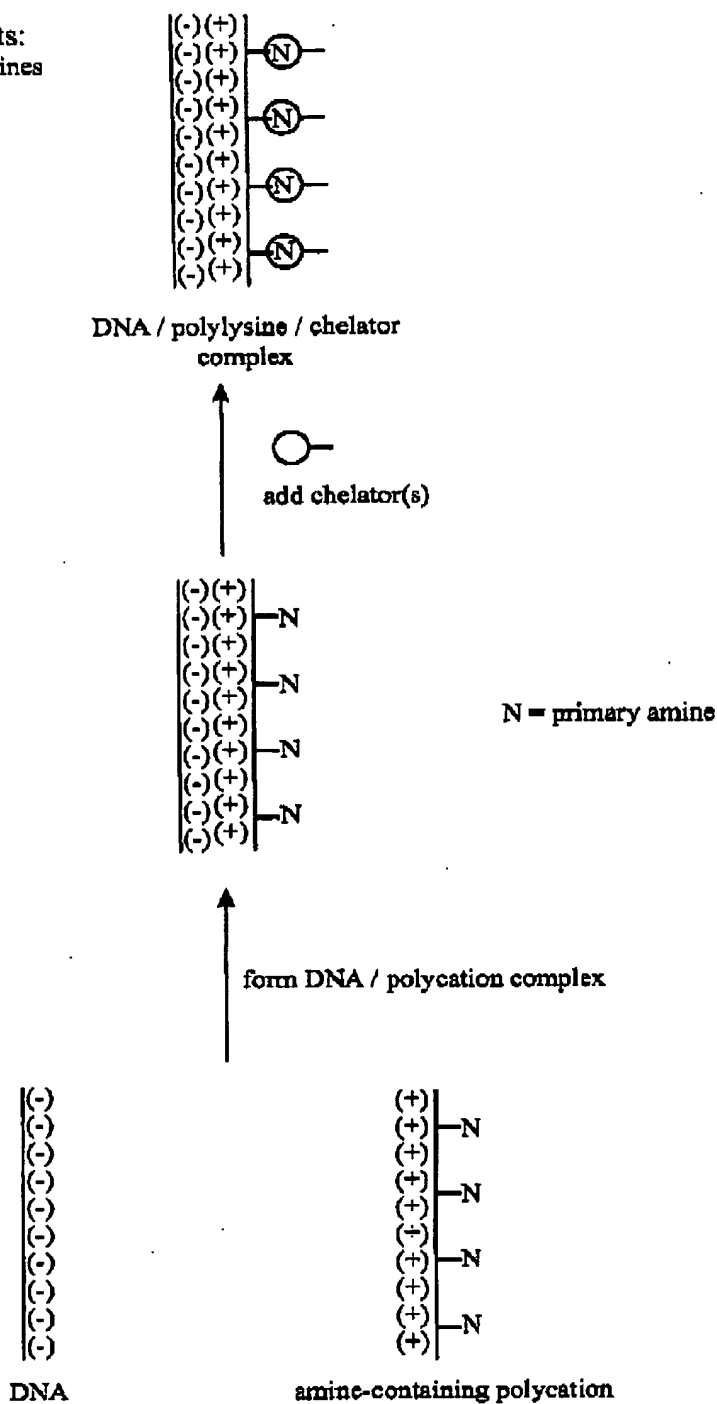
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Kirk Ekena

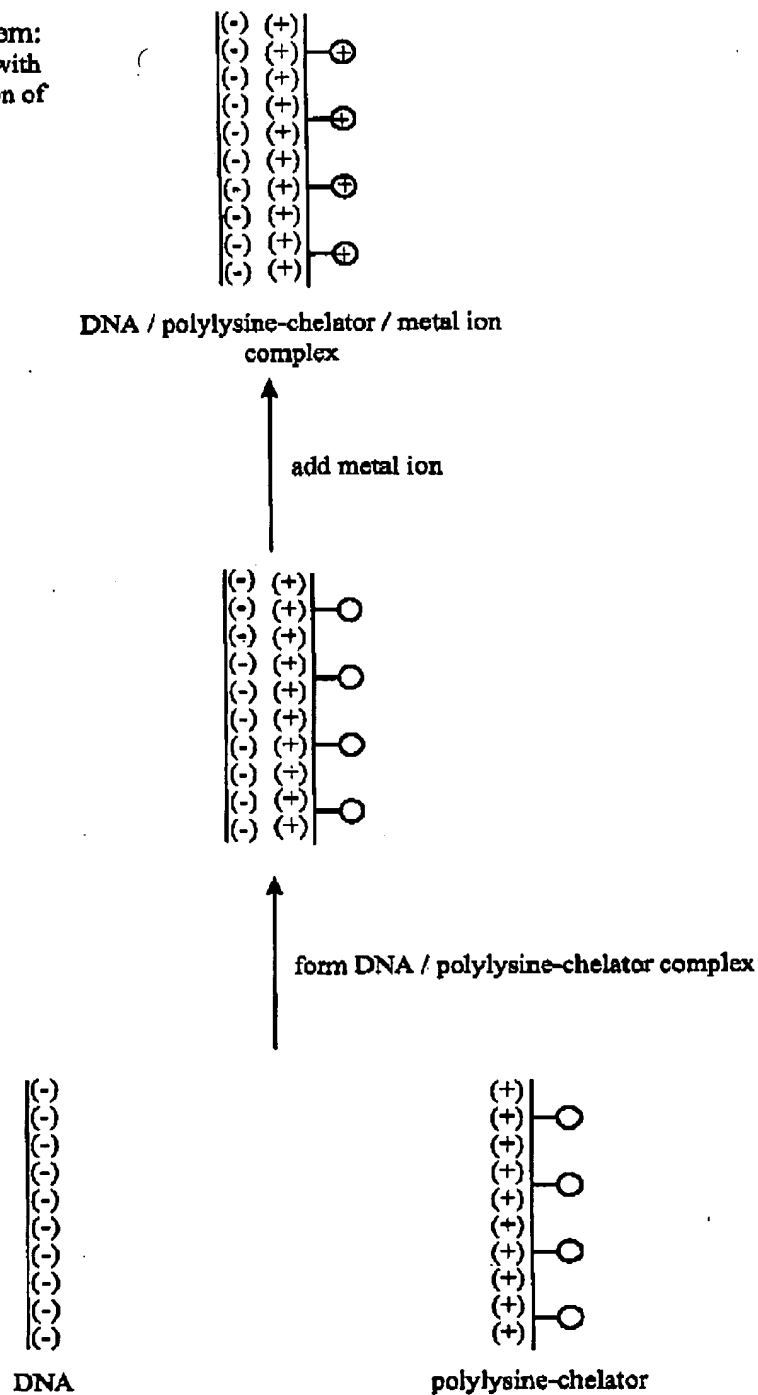
[REPLACEMENT SHEET]**CROSS-REFERENCE TO RELATED APPLICATIONS**

This application is a continuation of Application No. 09/234,606, filed January 21, 1999, now U.S. Patent 6,818,626, which claims the benefit of U.S. Provisional Application No. 60/093,230, filed July 17, 1998.

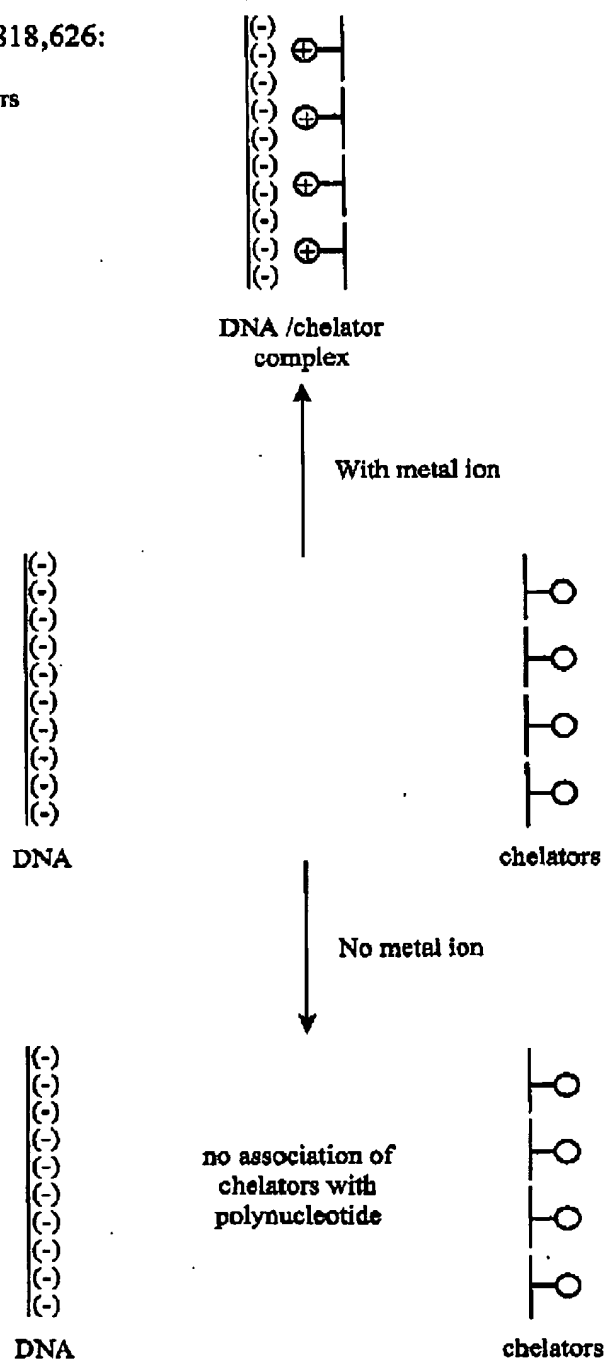
Method taught by Applicants:
association of chelators with amines
on polycations present in
polycation/DNA complexes



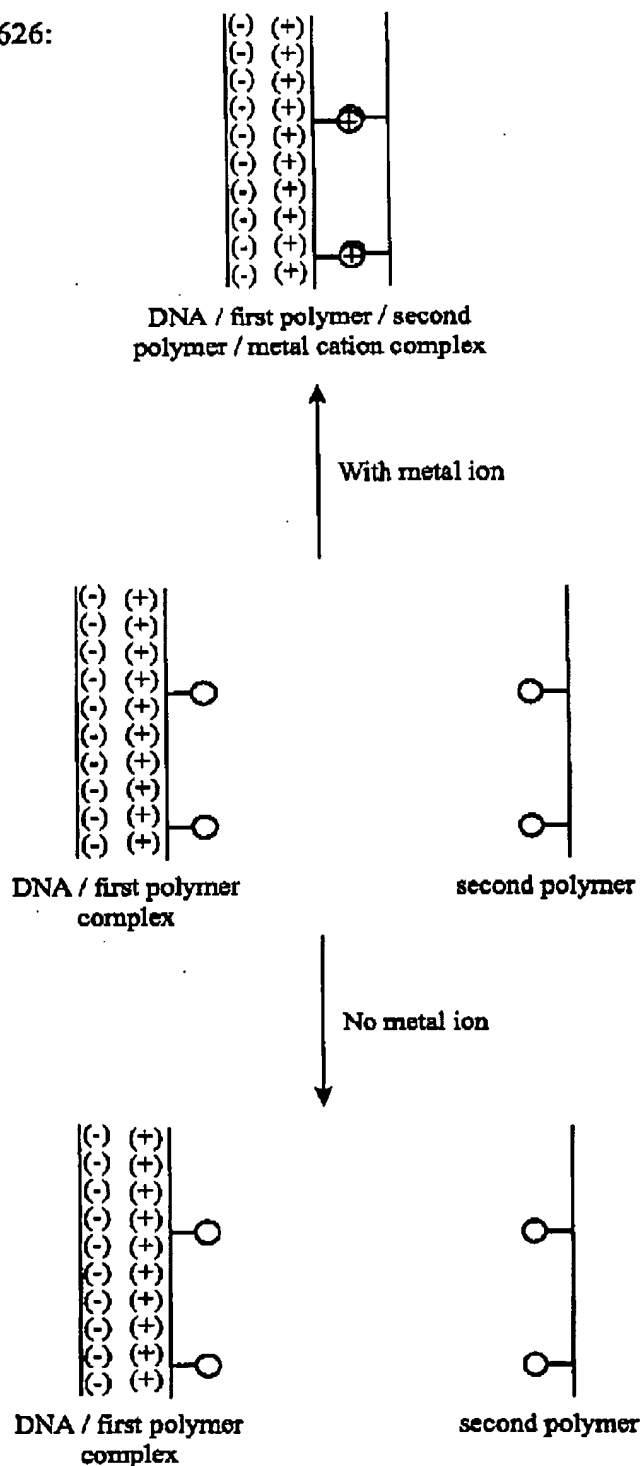
Method taught by Kayyem:
association of polychelator with
DNA followed by association of
metal ion with polychelator



Method claimed by 6,818,626:
metal cation dependent
association of two polymers
(claims 1-11)



Method claimed by 6,818,626:
metal ion dependent
association of two polymers
(claims 12-17)



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82 BONDING WEAKER THAN COVALENT

Unfortunately, salts of picric acid are also called picrates. Similar complexes are formed between phenols and quinones (quinaldehydes).⁵³ Oides that contain electron-withdrawing substituents also act as acceptor molecules as do carbon tetrachloride⁵⁴ and certain anhydrides.⁵⁵ A particularly strong olefin acceptor is tetraglyoxalene.⁵⁶

The bonding in these cases is more difficult to explain than in the previous case, and indeed no really satisfactory explanation is available.⁵⁷ The difficulty is that although the donor has a pair of electrons to contribute (both a donor and a donor are formed here), the acceptor does not have a vacant orbital. Simple attraction of the dipole-induced-dipole type accounts for some of the bonding⁵⁸ but is too weak to explain the bonding in all cases.⁵⁹ e.g., althothenes, with about the same dipole moment as nitrobenzene, forms much weaker complexes. Some other type of bonding clearly must also be present in many EDA complexes. The exact nature of this bonding, called *charge-transfer bonding*, is not well understood, but it presumably involves some kind of donor-acceptor interaction.

Crown Ether Complexes and Crystals⁶⁰

Crown ethers are large-ring compounds containing several oxygen atoms, usually in a regular pattern. Examples are 12-crown-4 (18),⁶¹ dipotassium-18-crown-6 (11), and 15-crown-5 (12). These compounds have the property⁶² of forming complexes with positive ions, Cs^+ .

For a review of crown ethers, see: Brown, *Encyclopedia of Chemistry*, 1974, 10, 101.

For a review of applications as ionophores, see: Brown, *Encyclopedia of Chemistry*, 1974, 10, 101.

For a review of complexes formed by ion-exchange resins and other polymeric compounds, see: Harty, *Report of the Chemistry of the Crown Group*, Wiley, New York, 1970, pp. 69-692. See also: Harty, *Encyclopedia of Chemistry*, 1974, 10, 101.

For a review, see: Brown, *Chem. Soc. Rev.*, 1974, 3, 493-500; Kasper, *Nature*, 1974, 248, 334-342; *Chem. Soc. Rev.*, 1974, 3, 493-500.

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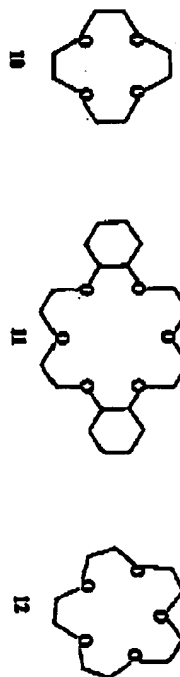
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CHAPTER 3

ADDITION COMPOUNDS 83

crally metallic ions (though not usually ions of transition metals) or ammonium and substituted ammonium ions.⁶³ The crown ether is called the *host* and the ion is the *guest*. In most cases the ions are held tightly in the center of the cavity.⁶⁴ Each crown ether binds



different ions, depending on the size of the cavity. For example, 10 binds Li^+ ⁶⁵ but not K^+ or Na^+ .⁶⁶ Similarly, 11 binds H_2O ⁶⁷ but not Cs^+ or Zn^{2+} , and S^{2-} but not Ca^{2+} .⁶⁸ The complexes can frequently be prepared as well-defined sharp melting solids.

Apart from their obvious utility in separating mixtures of cations,⁶⁹ crown ethers have found much use in organic synthesis (see the discussion on p. 363). Chiral crown ethers have been used for the resolution of racemic mixtures (p. 123). Although crown ethers are most frequently used to complex cations, anions, phenols, and other neutral molecules have also been complexed⁷⁰ (see p. 133 for the complexing of anions).⁷¹

Macrocycles containing nitrogen or sulfur atoms, e.g., 13 and 14,⁷² have similar properties, as do those containing more than one kind of hetero atom, e.g., 15,⁷³ 16,⁷⁴ or 17.⁷⁵ Bicyclic molecules like 16 can surround the nucleated ion in three dimensions, binding it even more tightly than the monocyclic crown ethers. Bicyclics and cycles of higher order⁷⁶ are called *cryptands* and the complexes formed are called *cryptates* (monocyclics are also sometimes called *cryptates*). The bicyclic cryptand 17 has ten binding sites and a spherical cavity.⁷⁷ Another molecule with a spherical, cavity (though not a cryptand) is 18, which

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ADDITION COMPOUNDS

molecular recognition.¹⁵ In general, cryptands, with their well-defined three-dimensional cavities, are better for this than monocyclic crown ethers or other derivatives. An example is the host 25, which selectively binds the dication 26 ($\alpha = 5$) rather than 26 ($\alpha = 4$), and 26 ($\alpha = 6$) rather than 26 ($\alpha = 7$).¹⁶ The host 27, which is water-soluble, forms 1:1 complexes

²This picture is taken from a paper by MICHAEL J. R. SOC. CHEN, 77, 1980, 1033.